

10 wherein:

D is branched or normal alkyl of 3 to 6 carbon atoms

E is H or CH₃

Z is H or CH₃

n is an integer from 3 to 8.

15 In addition to the modulus modifiers other well known hydrophobic monomers may be used in the formulation of the polymers employed in this invention to further tailor the properties to the particular application. The hydrophobic monomers useful in this invention also include monomers which contain at least one silicon or fluorine atom as a part of its composition. Examples of other hydrophobic monomers include alkyl, cyclo-alkyl and aryl acrylates and methacrylates as well as mono- or disubstituted itaconates, styrene and its derivatives, acrylonitrile, vinyl esters such as vinyl acetate or vinyl pentacetyl gluconate, vinyl ethers such as vinyl butyl ether, allyl esters such as allyl acetate, propionate or butyrate, fluorine containing monomers such as octafluoropentyl methacrylate and silicon containing monomer, e.g., 1,1,1-tris(trimethoxysiloxy)-3-methacryloxy-propylsilane or heptamethyltrisiloxanyl ethyl acrylate.

25 The monomeric mixtures, comprising the hydrophilic monomer(s), the modified or unmodified amino acid monomer(s), the optional hydrophobic monomer(s) and a cross-linking agent, are generally clear, colorless liquids of varying viscosity. These monomer mixtures can be readily cured to cast shapes by conventional methods such as free radical initiation.

As catalysts for carrying out the polymerization, there may be employed a free radical catalyst (initiator) in varying amounts and typically in the range of 0.05 % to 3 % w/w of the polymerizable monomer mixture. 30 The preferred amount of catalyst is 0.1% to 0.5% w/w of the total monomers present. Usually, the catalyst is added initially to the monomers and then the polymerization procedure is completed. The free radical type initiators suitable for this invention include peroxides, azo compounds, oxidation-reduction systems and similar initiators described in the literature. Typical catalysts include benzoin methyl ether, tertiary-butyl-peroxoate, benzoyl peroxide, isopropyl percarbonate, methyl ethyl ketone peroxide, cumene hydroperoxide, dicumyl peroxide, bis(isopropyl) peroxydicarbonate, 2,2'-azobis[isobutyronitrile], acetyl peroxide, lauroyl peroxide, decanoyl peroxide, 2,2'-azobis[2,4-dimethylvaleronitrile], phthalic peroxide, diethoxyacetophenone and tertiary-butyl peroxy-pivalate. Thermal catalysts, visible light or irradiation, e.g., by ultraviolet light or gamma rays, also can be employed to catalyze the polymerization. Polymerization can be done at 20 to 150°C, usually 40 to 90°C.

40 Water soluble diluents may be used to modify the physical properties of these polymers. More particularly, the diluents may be advantageous in improving machinability and swell characteristics of the polymer. Typically, the amount of diluent will be less than 50 weight percent of the total monomers employed and preferably not more than 30 weight percent. In a particular polymer system, the limiting amount of diluent is the solubility of the diluent in the monomer system. Thus, there should be no phase separation between diluent and starting monomer mixture. Additionally, excessive amounts of diluent will result in collapse of the cell structure of the finished biomedical devices when the device is hydrated, i.e., replacement of diluent by water. The maximum amount of diluent is readily ascertained by swelling the diluent free polymer in the proposed diluent and measuring the degree of swell. Comparable results are obtained when using solvent soluble diluents wherein the solvent does not affect the lens polymer. These solvents include ketones, e.g., methyl ethyl ketone and isopropyl alcohol. Suitable diluents include ethylene glycol, glycerin, liquid polyethylene glycols, butanol, butanol/water mixtures, ethylene oxide/propylene oxide block copolymers having a molecular weight from 1,000 to 5,000, linear poly(vinyl pyrrolidinone) having a molecular weight from 500 to 10,000, low molecular weight linear poly(hydroxyethyl methacrylate), glycol esters of lactic acid, formamide, dimethyl formamide, methyl ethyl ketone and dimethyl sulfoxide. In the finished biomedical device, it will be necessary to replace any diluent with an aqueous solution. With respect to contact lenses, the final water content of the polymeric composition typically ranges from 30% to 95% w/w. The contact lens should, of course, contain a physiological saline solution as the aqueous medium.

Using methods well known in the art, the sustained-release formulation of this invention can be formed into a variety of shapes depending upon the end use and desired results to be obtained therefrom. For ophthalmic purposes, the polymeric hydrogel could have any form to maintain direct contact with the eye. It is not necessary to cover the entire cornea if the dosage form is merely used to instill a continuous flow of an ophthalmic drug in the eye. If the hydrogel will also be used to correct vision, then it may be desirable to cast the polymer on an optical mold.

By way of example, the mixture of hydrophilic monomer(s), modified or unmodified amino acid monomer(s), cross-linking agent, free radical initiator and optional hydrophobic monomer(s) described above is purged with an inert gas such as nitrogen or carbon dioxide and filled into polypropylene tubes having dimensions of 18mm x 300 mm. The polymerization is then carried out by gradually heating from 30°C to 110°C in a step fashion over a span of several days. In a typical schedule the tubes are placed in a water bath from 30°C to 50°C for two to three days followed by two days at 60°C. The rod is then removed from the mold and post-cured at 110°C for a period of about four hours. The fully cured rods are then cut into cylinders, optionally then annealed at temperatures up to 150°C and machined to form contact lenses as desired. A spin-casting process as described in U.S. Patent Nos. 3,408,429 and 3,496,254 can be employed to prepare useful objects of this invention. The manufacturing technique may involve triple spin-casting or a casting method that does not involve spinning. Such static casting optionally may use polypropylene domes for lens shape and easy detachment from the lens surface. Of course, any conventional material which can give a proper lens shape would suffice.

This invention contemplates a variety of processes for preparing the sustained-release polymeric hydrogel dosage form whereby the medicinal agent is retained by the polymeric matrix and, upon tissue contact, is gradually released into the tissue. One process comprises incorporating the medicament directly into the monomer mixture and polymerizing the monomers in the presence of the drug to make a single homogeneous layer of polymer plus drug as the dosage form. Another process uses the drug-polymer layer as a middle layer in a "sandwich" dosage form in which two drug-free polymer layers are formed on either side of the middle layer containing the drug. Alternatively, a two layer system may be formed having one layer as polymer plus drug and the other layer as drug-free polymer. The amount of the drug used in the preparation of these dosage forms will vary depending upon the physicochemical properties of the selected drug and the therapeutic effect desired to be achieved. Typically, the drug is added on an equivalency basis, that is, an equivalent for equivalent basis of drug to the amino acid monomer. Although a stoichiometric number of equivalents of drug and the amino acid monomer is preferred, other amounts can also be used. As an example of pilocarpine hydrochloride, varying concentrations of the compound may be employed, desirably an amount from 0.5 % to 12 % w/w, and preferably 11.43 % w/w, for incorporation in the dosage form of choice.

In addition to the above dosage forms, the polymeric hydrogel of the instant invention may be prepared without the medicinal agent and then soaked in an aqueous solution of a therapeutically effective amount of the medicinal agent for a sufficient amount of time for equilibration. The amount of time for equilibration will vary depending on the physicochemical nature and concentration of the particular medicament solution. For example, the soaking time may be about 12 to 24 hours, preferably 24 hours, for a particular medicament such as pilocarpine hydrochloride at varying concentrations, desirably from 2 % to 8 % w/w.

Regardless of the exact mode of preparation, the polymeric composition provides appreciable time release of the medicament. The release rate varies with cross-linking density, type of polymer barrier system and mode of preparation. For example, a homogeneous layer of polymer plus drug may have a slower release profile than a polymer soaked in a drug solution. Likewise, a layering technique may provide an even slower release profile than the homogeneous layer of polymer plus drug.

To quantify the release rates, lenses with and without drug can be placed in a known quantity of release media (distilled water or buffered saline) and stirred with a magnetic stirrer. At various times the lenses can be transferred to fresh media and the absorbance of the previous media can be determined by ultraviolet spectroscopy. The absorbance of the media containing druged lenses is reduced by the absorbance of the media containing undrugged lenses. Use of a calibration curve relating absorbance to concentration allows for a determination of the concentration of the drug. The calibration curve is developed by measuring the absorbance of known concentrations of the drug in the release media. As the concentrations ($\mu\text{g/ml}$) of the drug and the volume (ml) of release media are known, the amount of the released drug can be calculated (μg). This value divided by the time of exposure to the media gives the release rate in $\mu\text{g/hr}$ which is plotted against time.

For illustration, a sustained-release "sandwich" dosage form prepared with about 12 % w/w of pilocarpine hydrochloride in the middle layer would release the drug in distilled water initially at a rate of about 5 $\mu\text{g/hour}$ and by around 40 hours at a constant rate of about 0.5 $\mu\text{g/hour}$. Using the soaking

technique for about 24 hours produced a subsequent constant release rate in distilled water of approximately $5 \mu\text{g}/\text{hour}$ to approximately $20 \mu\text{g}/\text{hour}$.

Contact lenses made from the polymer utilized in the instant invention are oxygen permeable. A critical oxygen tension and flux under a lens should be about 10 mm Hg and $2 \mu\text{l}/(\text{cm}^2\text{hr.})$ respectively below which corneal swelling occurs, see Polse and Decker, Investigative Ophthalmology and Visual Science, 18:188 (1979). In order to meet these requirements, the lens material must have adequate oxygen permeability. These more preferred contact lenses have an oxygen permeability of at least about $24 \times 10^{-11} \text{ cm}^3\text{cm}/(\text{sec.cm}^2\text{mmHg})$, are hydrolytically stable, biologically inert and transparent. In comparison, the well-known contact lens polymer polyhydroxyethyl methacrylate has an oxygen permeability value of about one-third of this value.

Additionally, these lenses are hydrolytically stable, meaning that when the contact lenses are placed into an aqueous solution (e.g., on the eye) or during the disinfecting step (i.e., water plus heat), the lenses will not change in chemical composition. That is, they will not hydrolyze. On heating in boiling water for 120 hours, the typical polymer of this invention experiences a water content loss of 3% or less. The most preferred lenses/polymers useful in this invention have a stable water content that undergoes less than 1% change. Thus, the polymers and copolymers disclosed herein can be boiled and/or autoclaved in water without being damaged whereby sterilization may be achieved. In addition sterilization can be achieved by gamma-irradiation, ultraviolet light irradiation and ethylene oxide exposure.

The polymers and copolymers employed in this invention being soft yet resilient and hard to tear are well suited for preparing biomedical devices, including contact lenses, which have the ability to release medications from the polymeric matrix over a prolonged period of time. It is well known that the wearer of soft contact lenses will have an unavoidable amount of handling of the lenses. Part of the cleaning and rinsing procedure is to rub each lens and tearing has been a concern in prior art lenses. The polymers and copolymers used in the present invention have a tear initiation strength (ASTM D-1938) of up to 5 g/mm of thickness.

An article formed from the disclosed polymers and copolymers may be used to administer medications to mammals where an article compatible with living tissue or with the mucous membranes is desired. The term "biomedical devices" means the materials disclosed herein have nontoxic, nonirritating physiochemical properties rendering them suitable for prolonged contact with living tissue, blood and the mucous membranes. It is known that blood, for example, is rapidly damaged in contact with artificial surfaces. The design of a synthetic surface which is antithrombogenic and nonhemolytic to blood is necessary for drug administering devices used with blood, especially an implanted or transdermal device. The polymers and copolymers employed for the purposes of the instant invention are compatible with living tissue.

The instant invention provides a novel sustained-release polymeric hydrogel dosage form useful for topical, systemic or transdermal administration of a medicinal agent comprising the above-described polymeric matrix in association with a therapeutically effective amount of the medicinal agent. The specific polymeric matrix containing an amino acid polymer permits the subsequent release of the active ingredient at a gradual, carefully controlled rate prolonging the time release period. In contrast to normal disintegration time, the sustained-release administration of medicaments enhances therapeutic effectiveness and decreases many undesirable side effects by maintaining constant tissue and blood levels.

The polymeric hydrogel dosage form can be used in preparing biomedical devices that upon surgical implant will provide sustained-release activity of the active ingredient. Depending on the location of the implant, the therapeutic effect may be local or systemic. The dosage form can also provide for the topical (i.e., localized activity on the skin) controlled-release administration of medicaments. Additionally, the dosage form can be utilized for the transdermal controlled-release administration of medicaments, i.e., the device is retained in contact with the skin for transdermal absorption of the medicament into the blood for systemic effect. Contact with the skin may be achieved by any means well-known in the art such as by incorporating an adhesive in or on the device, adhering the device within or onto a bandage-type articles.

Further, the dosage form can be useful for the ophthalmic route of administering medicinal agents for either local or systemic therapeutic effect. The term "ophthalmic administration of a systemic medicament" defines the administration of a medicinal agent to a mammal by the ophthalmic route whereby the medicinal agent acts therapeutically to create a systemic effect. For ophthalmic administration of a medicament to produce local or systemic activity, the polymeric composition can be molded into any convenient shape for eye contact. If correcting vision is not necessary, the dosage form does not have to cover the entire cornea. Alternatively, the polymeric hydrogel can be shaped into contact lenses on optical molds if it is desirable to correct vision in addition to administer ophthalmic medicaments.

The length of time for contacting the polymeric hydrogel device containing a medicament with a tissue of a mammal depends upon the individual circumstances of each case. A sufficient amount of time to

achieve a constant therapeutic effect varies in accordance with the optimum therapeutic effect desired. The duration of therapy is, of course, contingent upon the disease or medical problem being treated or palliated. Likewise, the therapeutically effective amount of the specific medicinal agent is determined by therapy requirements and the biophysical properties of the active compound. For example, with respect to contact lenses, the invention contemplates daily wear or extended wear, typically, up to a month. To treat an eye infection, it would be desirable to maintain the contact lens containing an antibiotic or an antiviral agent on the eye for one to two weeks. On the other hand, to treat glaucoma, it would be desirable to wear the lens containing an agent for reducing intraocular pressure for the maximum time that extended wear contact lenses can remain in the eye.

The term "dosage form" refers to physically discrete units suitable as unitary dosage for mammals, each unit containing a predetermined quantity of medicinal agent calculated to produce the desired therapeutic effect.

The term "medicinal agent" means a substance used in treating or ameliorating a disease or medical condition. For purposes of this invention, "medicinal agent" refers to drugs which have the capacity to be bound to the amino acid moiety of the polymeric hydrogel. That is, any drug or its salt with polar characteristics that interacts with amino acids in a favorable way can be used in the present invention. Examples of medicinal agents include antibiotics, antivirals, anti-inflammatories, steroids, peptides, polypeptides, cardiotonics, antihypertensives, antiallergics, alpha- and beta-adrenergic blocking agents, anticataract agents, ophthalmic medicaments, ophthalmic lubricating agents, ophthalmic topical or regional anesthetic agents. The ophthalmic medicaments or other medicinal agents encompass such drugs as pilocarpine, idoxuridine, carbachol, bethanechol, timolol, tetracycline, epinephrine, phenylephrine, eserine, phospholine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerin, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin, erythromycin, sulfacetamide, polymyxin B, tobramycin, isofluorophate, fluoromethalone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone, methyl prednisolone, betamethasone, triamcinolone, interferon, cromolyn and all-trans-retinoic acid (Vitamin A), and the nontoxic, pharmaceutically acceptable salts thereof. The category of ophthalmic lubricating agents refers to those agents capable of inducing natural lacrimation or creating artificial lacrimation and includes, for example, polyvinyl alcohol, cellulose polymers such as hydroxypropyl methyl cellulose, a polylactam such as polyvinyl pyrrolidinone and other tear inducers or substitutes. The topical or regional anesthetic agents, which may be useful during ophthalmic surgery or other ophthalmic procedures, include lidocaine, cocaine, benoxinate, dibucaine, proparacaine, tetracaine, etidocaine, procaine, hexylcaine, bupivacaine, mepivacaine, prilocaine and chloroprocaine.

The term "pharmaceutically acceptable salt" refers to those salts of the parent compound which do not significantly or adversely affect the pharmaceutical properties (e.g., toxicity, efficacy,) of the parent compound. The salts of the present invention which are pharmaceutically acceptable include, for example, chloride, iodide, bromide, hydrochloride, acetate, nitrate, stearate, phosphate and sulfate. It is desirable to use the appropriate salt form of the active ingredient which would increase the water solubility or polar characteristics of the base compound.

The following examples illustrate the present invention. All parts and percents referred to herein are on a weight basis and all temperatures are expressed in degrees Celsius unless otherwise specified. The procedures described were conducted at room temperature (about 23°C to about 28°C) and at atmospheric pressure unless otherwise specified.

EXAMPLE 1

Preparation of Hydrogel Polymer

A clear, homogeneous solution is prepared by mixing together 83.5 g of 2-hydroxyethyl methacrylate (HEMA), 10 g of isobornyl methacrylate (IBOMA), 6 g of methacroyl glycine (MG) and 0.5 g of ethylene glycol dimethacrylate (EGDMA). To the mixture is added 0.5 g of benzoin methyl ether (BME). The clear solution of monomers (A) is polymerized under hot ultraviolet light (UV) for 15 minutes against a suitable optical mold under an inert atmosphere. Water content is about 60%.

EXAMPLE 2

Soaking Method

The procedure of Example 1 is repeated to prepare the hydrogel polymer. The polymer is soaked in an

aqueous solution of 4% w/w pilocarpine hydrochloride for 24 hours.

EXAMPLE 3

5 Preparation of Single-Layer Hydrogel Polymer Containing Medicament

Solution A is prepared in accordance with the procedure of Example 1. To the solution is added 11.43 g of pilocarpine hydrochloride. The clear, homogeneous solution (B) is placed on a suitable spincoating optical mold. It is spin cast under UV and nitrogen for 40 minutes.

EXAMPLE 4

Preparation of Triple-Layer Hydrogel Polymer Containing Medicament

15 Solutions A and B are prepared in accordance with the respective procedures of Examples 1 and 3. On a suitable spincoating optical mold is injected 9.8 μ l of solution A and is spin cast under UV and nitrogen for 5 minutes at 300 rpm. On the resulting polymer is injected 29.4 μ l of solution B. Spin casting is repeated in the same manner as for the first layer. On the second polymer layer is injected 9.8 μ l of solution A. The same spin casting technique is again repeated. The result is a triple-pun contact lens with a polymer-drug layer encapsulated between two polymer layers without the drug.

EXAMPLE 5

Release Studies I

25 The procedure of Example 1 is repeated to prepare the hydrogel polymer. The polymer, Ocusert-20®, Ocusert-40® and Permalens® are separately soaked in an aqueous solution of 4 % w/w pilocarpine hydrochloride for 17 hours. Each lens is then separately placed in distilled water with stirring. With appropriate controls, the release rate of the drug into the water is measured. The results are shown in 30 Figures 1-4 illustrating the release characteristics of the hydrogel polymer used in this invention, Ocusert-20®, Ocusert-40® and Permalens®, respectively. A percent release comparison of the Permalens® and the hydrogel polymer is set forth in Figure 8. The raw data release characteristics obtained by this experiment are supplied in Figures 9, 10 and 13.

35 Example 6

Release Studies II

40 The procedure of Example 1 is repeated to prepare two hydrogel polymers. The two polymers and two Soflens® lenses (polymacon soft contact lens available from Bausch & Lomb) are separately soaked in an aqueous solution of 4 % w/w pilocarpine hydrochloride for 17 hours. One of each type of lens is placed in buffered saline and distilled water respectively. The Soflens® released all the drug present in 1-1/2 hours and 2-1/2 hours in the buffered saline and distilled water respectively. The release characteristics of the polymers are illustrated in Figures 5 and 6 for the respective distilled water and buffered saline tests. The 45 raw data release characteristics are illustrated in Figures 11 and 12.

Example 7

Release Studies III

50 The procedure of Example 4 is repeated to prepare a triple-layer hydrogel polymer containing pilocarpine hydrochloride. The polymer is placed in distilled water and the release rate is measured. The results are shown in Figure 7 illustrating the release characteristics of the product of Example 4.

55 Claims

1. A sustain d-releas polym ric hydrogel dosage form useful for topical, systemic or transdermal administration of a m dicinal agent comprising a cross-linked hydrophilic polymer containing units

- derived from amino acid monomer, and said medicinal agent in a therapeutically effective amount releasably bound to amino acid groups of said polymer.
2. The sustained-release dosage form of Claim 1, wherein the polymer includes therein units derived from a hydrophobic monomer.
 3. The sustained-release dosage form of Claim 1 or 2, wherein the amino acid monomer is methacroyl glycine, methacroyl glutamate, methacroyl desmosine or methacroyl isodesmosine.
 4. The sustained-release dosage form of any preceding claim wherein said medicinal agent is an antibiotic, an antiviral, an anti-inflammatory, a steroid, a peptide, a polypeptide, a cardiotonic, an antihypertensive, an antiallergic, an alpha-adrenergic blocking agent, a beta-adrenergic blocking agent, an anti-cataract agent, an ophthalmic medicament, an ophthalmic lubricating agent or an ophthalmic anesthetic agent.
 5. The sustained-release dosage form of any preceding claim, wherein said medicinal agent is selected from pilocarpine, idoxuridine, carbachol, bethanechol, timolol, tetracycline, epinephrine, phenylephrine, eserine, phospholine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerin, chlor-tetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin, erythromycin, sulfacetamide, polymyxin B, tobramycin, isofluorophate, fluoromethalone, dex-amethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone, methyl prednisolone, be-tamethasone, triamcinolone, interferon, cromolyn and all trans-retinoic acid and the nontoxic, phar-maceutically acceptable salts thereof.
 6. The sustained-release dosage form of Claim 4, wherein said medicinal agent is an ophthalmic lubricating agent selected from polyvinyl alcohol, a cellulose polymer and a polyactam.
 7. The sustained-release dosage form of any preceding claim, wherein said dosage form is molded as a contact lens or ocular insert for ophthalmic administration of a systemic medicament, an ophthalmic medicament or an ophthalmic lubricating agent.
 8. The sustained-release dosage form of Claim 7, wherein said dosage form is molded as a contact lens which has the ability to correct vision.
 9. The sustained-release dosage form of any preceding claim, wherein the polymeric hydrogel is prepared from a polymerizable hydrophilic monomer present in the amount of 50% to 90% w/w, an amino acid monomer present in the amount of 5% to 27% w/w, a cross-linking agent present in the amount of 0.1% to 20% w/w and a hydrophobic monomer present in the amount of 8% to 20% w/w, said weight percentages being based on the total weight of the polymeric hydrogel.
 10. A process for the preparation of the sustained-release dosage form of Claim 1 or Claim 2 which comprises preparing a homogeneous solution or suspension by mixing a hydrophilic monomer, an amino acid monomer, optionally a hydrophobic monomer a cross-linking agent and a medicinal agent, and polymerizing the solution or suspension.
 11. A process for the preparation of the sustained-release dosage form of Claim 1 or Claim 2 which comprises preparing a homogeneous solution A by mixing a hydrophilic monomer, an amino acid monomer, optionally a hydrophobic monomer, and a cross-linking agent; preparing a homogeneous solution or suspension B by mixing the hydrophilic monomer, the amino acid monomer, optionally the hydrophobic monomer, the cross-linking agent and a medicinal agent; polymerizing a portion of solution A; polymerizing solution or suspension B on top of polymerized solution A; and polymerizing remainder of solution A on top of polymerized solution or suspension B.
 12. A process for the preparation of the sustained-release dosage form of Claim 1 or Claim 2 which comprises preparing a homogeneous solution by mixing a hydrophilic monomer, an amino acid monomer, optionally a hydrophobic monomer, and a cross-linking agent, polymerizing the solution into a polymer and soaking the polymer in an aqueous solution or suspension of a medicinal agent for a sufficient amount of time for equilibration.

13. The process of any one of Claims 10-12, wherein a catalyst is used.
14. The process of Claim 13, wherein a mold is used.
15. The process of any one of Claim 13, wherein the polymerizing step involves spin casting.

Revendications

1. Forme de conditionnement d'un hydrogel polymère à libération progressive destinée à l'administration topique, systémique ou transdermique d'un agent médicinal comportant un polymère hydrophile réticulé contenant des motifs dérivés d'un acide aminé monomère et cet agent médicinal en quantité efficace lié de façon à pouvoir se dégager, aux groupes acides aminés de ce polymère.
2. La forme de conditionnement à libération progressive de la revendication 1, dans laquelle le polymère comprend des motifs dérivés d'un monomère hydrophobe.
3. La forme de conditionnement à libération progressive de la revendication 1 ou 2, dans laquelle le monomère d'acide aminé est un dérivé de la méthacroyle-glucine, du glutamate de méthacroyle, de la méthacroyle desmosine ou de la méthacroyle-isodesmosine.
4. La forme de conditionnement à libération progressive de l'une quelconque des revendications précédentes, dans laquelle l'agent médicinal est un antibiotique, un anti-viral, un anti-inflammatoire, un stéroïde, un peptide, un polypeptide, un cardiotonique, un anti-hypertension, un anti-allergique, un agent bloquant α -adrénergique, un agent bloquant β -adrénergique, un agent anti-cataracte, un médicament ophtalmique, un agent lubrifiant ophtalmique, ou un agent anesthésiant ophtalmique.
5. La forme de conditionnement à libération progressive selon l'une quelconque des revendications précédentes, dans laquelle ledit agent médicinal est choisi parmi la pilocarpine, l'idoxuridine, le carbachol, le bethanecol, le timolol, la tétracycline, l'épinéphrine, la phényléphrine, l'ésérine, la phospholine, le démécarium, le cyclopentolate, l'homatropine, la scopolamine, la nitroglycérine, la chloro-tétracycline, la bacitracine, la néomycine, la polymyxine, la gramicidine, l'oxy-tétracycline, le chloramphénicol, la gentamycine, la pénicilline, l'érythromycine, le sulfacétamide, la polymyxine B, la tobramycine, l'isofluorophosphate, la fluorométhalone, la dexaméthasone, l'hydrocortisone, la fluorocinolone, la médrysone, la prédnisolone, la méthyl-prédnisolone, la β -méthazone, la triamcinolone, l'interféron, la cromolyne et tous les acides trans-rétiniens, et leurs sels non toxiques, pharmaceutiquement acceptables.
6. La forme de conditionnement à libération progressive de la revendication 4, dans laquelle ledit agent médicinal est un agent de lubrification ophtalmique choisi parmi l'alcool polyvinylique, un polymère de la cellulose ou un polylactame.
7. La forme de conditionnement à libération progressive selon l'une quelconque des revendications précédentes, dans laquelle cette forme est moulée comme une lentille de contact ou un insert oculaire pour l'administration ophtalmique d'un médicament systémique, d'un médicament ophtalmique ou d'un agent de lubrification ophtalmique.
8. La forme de conditionnement à libération progressive selon la revendication 7, dans laquelle ladite forme est moulée sous forme d'une lentille de contact apte à corriger la vue.
9. La forme de conditionnement à libération progressive selon l'une quelconque des revendications précédentes, dans laquelle l'hydrogel polymère est préparé à partir d'un monomère hydrophile polymérisable présent à raison de 50 à 90 % en poids, d'un acide aminé présent à raison de 5 à 27% en poids, d'un agent de réticulation présent à raison de 0,1 à 20% en poids, et d'un monomère hydrophobe présent à raison de 8 à 20% en poids, ces pourcentages en poids étant basés sur le poids total de l'hydrogel polymère.
10. Procédé de préparation de la forme de conditionnement à libération progressive de la revendication 1 ou de la revendication 2, qui comprend la préparation d'une solution ou d'une suspension homogène

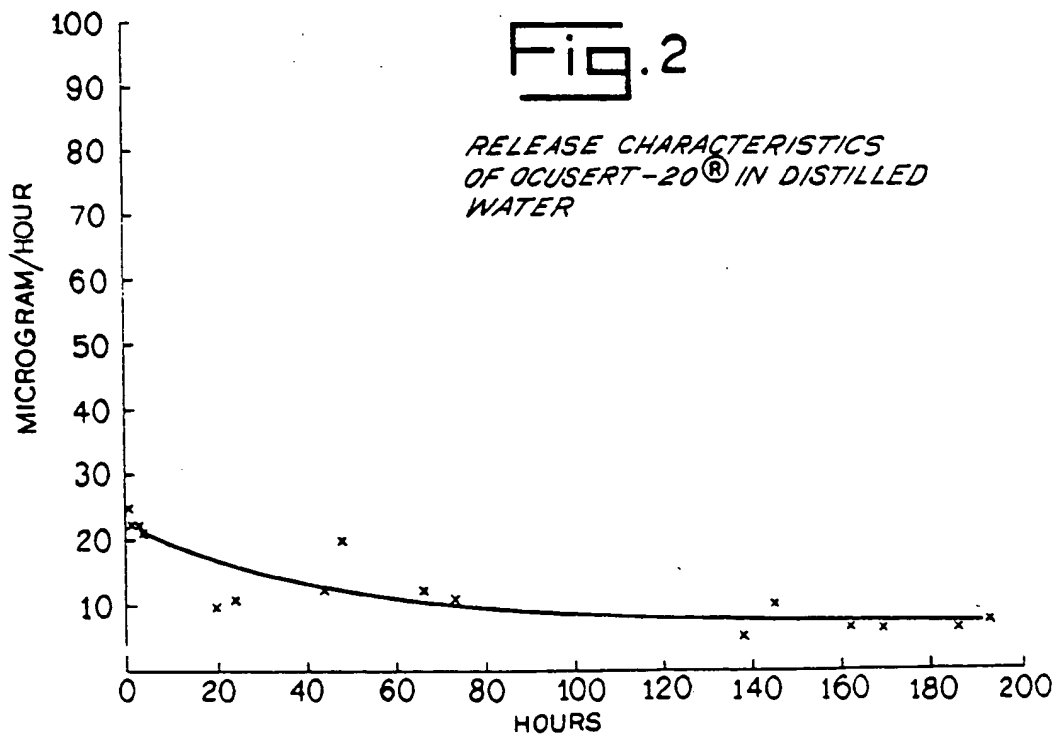
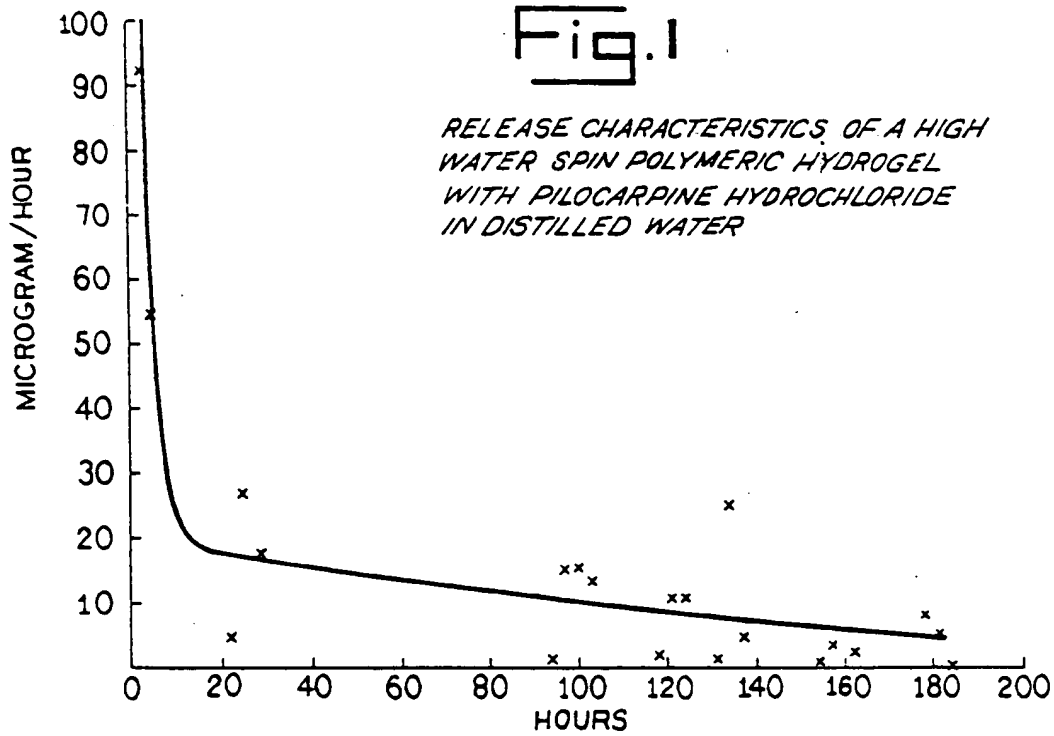
par mélange d'un monomère hydrophil, d'un acide aminé monomère, optionnellement d'un monomère hydrophobe, d'un agent de réticulation et d'un agent médicinal, suivi par la polymérisation de la solution ou de la suspension.

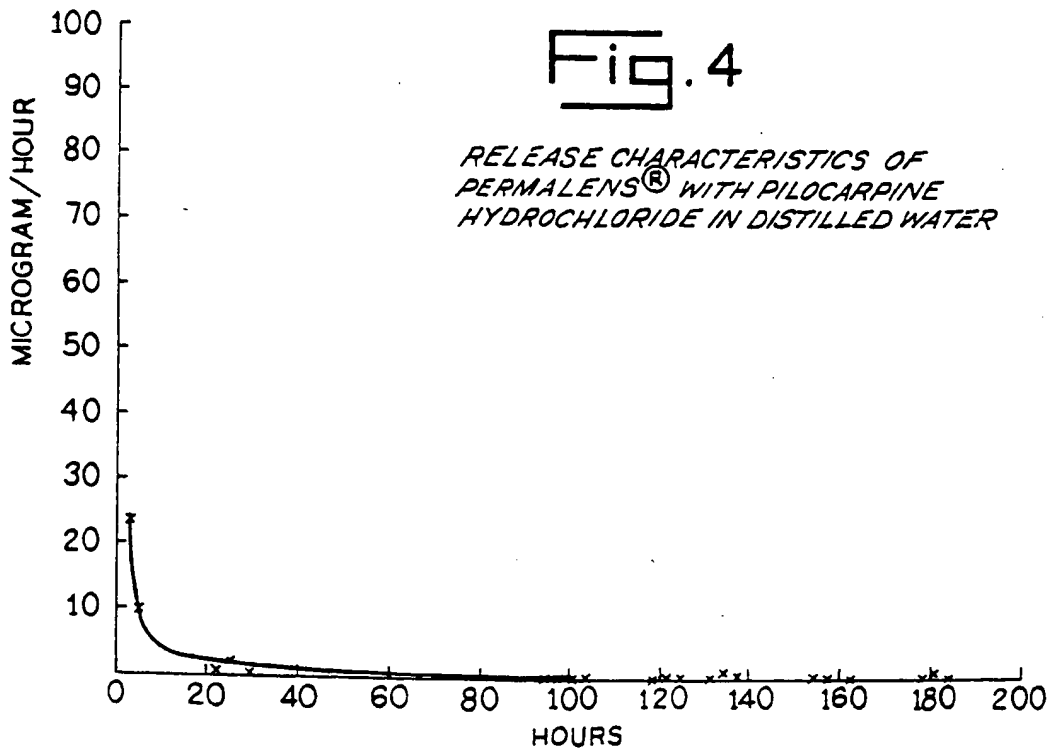
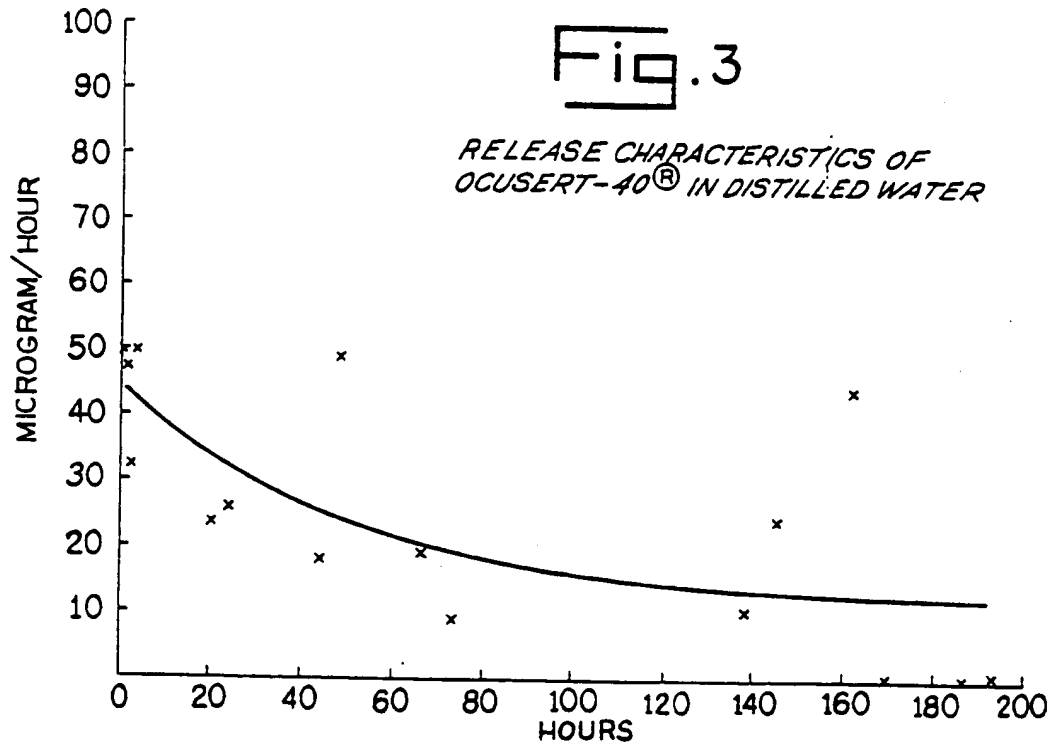
- 5 11. Procédé de préparation de la forme de conditionnement à libération progressive de la revendication 1 ou de la revendication 2, qui comprend
 - la préparation d'une solution homogène A par mélange d'un monomère hydrophile, d'un acide aminé monomère, optionnellement d'un monomère hydrophobe, et d'un agent de réticulation ;
 - 10 - préparation d'une solution ou d'une suspension homogène B par mélange du monomère hydrophile, de l'acide aminé monomère, optionnellement du monomère hydrophobe, de l'agent de réticulation et d'un agent médicinal ;
 - polymérisation d'une partie de la solution A ; polymérisation de la solution ou de la suspension B sur la solution A polymérisée ; et polymérisation du reste de la solution A sur la solution ou la suspension polymérisée B.
- 15 12. Procédé de préparation de la forme de conditionnement à libération progressive de la revendication 1 ou de la revendication 2, qui comprend
 - la préparation d'une solution homogène par mélange d'un monomère hydrophile, optionnellement d'un monomère hydrophobe, et d'un agent de réticulation ;
 - 20 - polymérisation de la solution pour donner un polymère et
 - immersion du polymère dans une solution ou une suspension aqueuse d'un agent médicinal pendant un temps suffisant pour atteindre l'équilibre.
- 25 13. Le procédé de l'une quelconque des revendications 10 à 12, dans lequel on utilise un catalyseur.
14. Le procédé de la revendication 13, selon lequel on utilise un moule.
15. Le procédé de la revendication 14, selon lequel l'étape de polymérisation comprend une coulée centrifuge.

Patentansprüche

1. Polymere Hydrogeldosierungsform mit Langzeitwirkung, die für die topische, systemische oder transdermale Verabreichung eines Arzneimittels geeignet ist und ein vernetztes hydrophiles Polymer umfaßt, das sich von Aminosäuremonomer ableitende Einheiten und das Arzneimittel, das freisetzbar an Aminogruppen des Polymers gebunden ist, in einer therapeutisch wirksamen Menge enthält.
2. Dosierungsform mit Langzeitwirkung nach Anspruch 1, bei der das Polymer Einheiten enthält, die sich von einem hydrophoben Monomer ableiten.
3. Dosierungsform mit Langzeitwirkung nach Anspruch 1 oder 2, bei der das Aminosäuremonomer Methacroylglycin, Methacroylglutamat, Methacroyldesmosin oder Methacroylisodesmosin ist.
4. Dosierungsform mit Langzeitwirkung nach einem der vorhergehenden Ansprüche, bei der das Arzneimittel ein Antibiotikum, ein Antivirumittel, ein entzündungshemmendes Mittel, ein Steroid, ein Peptid, ein Polypeptid, ein Kardiotonikum, ein Antihypertensivum, ein Antiallergikum, ein α -Blocker, ein β -Blocker, ein Antikataraktmittel, ein ophthalmisches Medikament, ein ophthalmisches Schmiermittel oder ein ophthalmisches Anästhetikum ist.
5. Dosierungsform mit Langzeitwirkung nach einem der vorhergehenden Ansprüche, bei der das Arzneimittel ausgewählt ist aus Pilocarpin, Idoxuridin, Carbachol, Bethanechol, Timolol, Tetracyclin, Epinephrin, Phenylephrin, Eserin, Phospholin, Demecarium, Cyclopentolat, Homatropin, Scopolamin, Nitroglycerin, Chlortetracyclin, Bacitracin, Neomycin, Polymyxin, Gramicidin, Oxytetracyclin, Chloramphenicol, Gentamycin, Penicillin, Erythromycin, Sulfacetamid, Polymyxin B, Tobramycin, Fluostigmin, Fluoromethalon, Dexamethason, Hydrocortison, Fluorocinolone, Medrysone, Prednisolon, Methylprednisolon, Betamethason, Triamcinolon, Interalon, Cromolyn und all trans-Retinsäure, sowie die nicht-toxischen, pharmazeutisch akzeptablen Salze derselben.

6. Dosierungsform mit Langzeitwirkung nach Anspruch 4, bei der das Arzneimittel ein ophthalmisches Schmiermittel aus wählt aus Polyvinylalkohol, einem Cellulosepolymer und einem Polylactam ist.
7. Dosierungsform mit Langzeitwirkung nach einem der vorhergehenden Ansprüche, bei der die Dosierungsform als Kontaktlinse oder Okulareinsatz für die ophthalmische Verabreichung eines systemischen Medikaments, eines ophthalmischen Medikaments oder eines ophthalmischen Schmiermittels geformt ist.
8. Dosierungsform mit Langzeitwirkung nach Anspruch 7, bei der die Dosierungsform als Kontaktlinse geformt ist, die die Fähigkeit hat, das Sehvermögen zu korrigieren.
9. Dosierungsform mit Langzeitwirkung nach einem der vorhergehenden Ansprüche, bei der das polymere Hydrogel aus einem in einer Menge von 50 bis 90 % Gewicht/Gewicht vorhandenen polymerisierbaren, hydrophilen Monomer, einem in einer Menge von 5 bis 27 % Gewicht/Gewicht vorhandenen Aminosäuremonomer, einem in einer Menge von 0,1 bis 20 % Gewicht/Gewicht vorhandenen Vernetzungsmittel und einem in einer Menge von 8 bis 20 % Gewicht/Gewicht vorhandenen, hydrophoben Monomer hergestellt worden ist, wobei diese Gewichtsprozentage auf das Gesamtgewicht des polymeren Hydrogels bezogen sind.
10. Verfahren zur Herstellung der Dosierungsform mit Langzeitwirkung nach Anspruch 1 oder Anspruch 2, bei dem eine homogene Lösung oder Suspension hergestellt wird, indem ein hydrophiles Monomer, ein Aminosäuremonomer, gegebenenfalls ein hydrophobes Monomer, ein Vernetzungsmittel und ein Arzneimittel gemischt werden, und die Lösung oder Suspension polymerisiert wird.
11. Verfahren zur Herstellung der Dosierungsform mit Langzeitwirkung nach Anspruch 1 oder Anspruch 2, bei dem eine homogene Lösung A hergestellt wird, indem ein hydrophiles Monomer, ein Aminosäuremonomer, gegebenenfalls ein hydrophobes Monomer, ein Vernetzungsmittel gemischt werden, eine homogene Lösung oder Suspension B hergestellt wird, indem das hydrophile Monomer, das Aminosäuremonomer, gegebenenfalls das hydrophobe Monomer, das Vernetzungsmittel und ein Arzneimittel gemischt werden, ein Teil von Lösung A polymerisiert wird, die Lösung oder Suspension B auf die polymerisierte Lösung A polymerisiert wird und der Rest von Lösung A auf die polymerisierte Lösung oder Suspension B polymerisiert wird.
12. Verfahren zur Herstellung der Dosierungsform mit Langzeitwirkung nach Anspruch 1 oder Anspruch 2, bei dem eine homogene Lösung hergestellt wird, indem ein hydrophiles Monomer, ein Aminosäuremonomer, gegebenenfalls ein hydrophobes Monomer und ein Vernetzungsmittel gemischt werden, die Lösung zu einem Polymer polymerisiert wird und das Polymer in einer wäßrigen Lösung oder Suspension eines Arzneimittels für einen zur Gleichgewichtseinstellung ausreichenden Zeitraum eingebracht wird.
13. Verfahren nach einem der Ansprüche 10 bis 12, bei dem ein Katalysator verwendet wird.
14. Verfahren nach Anspruch 13, bei dem ein Form verwendet wird.
15. Verfahren nach Anspruch 13, bei dem der Polymerisierungsschritt Schleudergießen umfaßt.





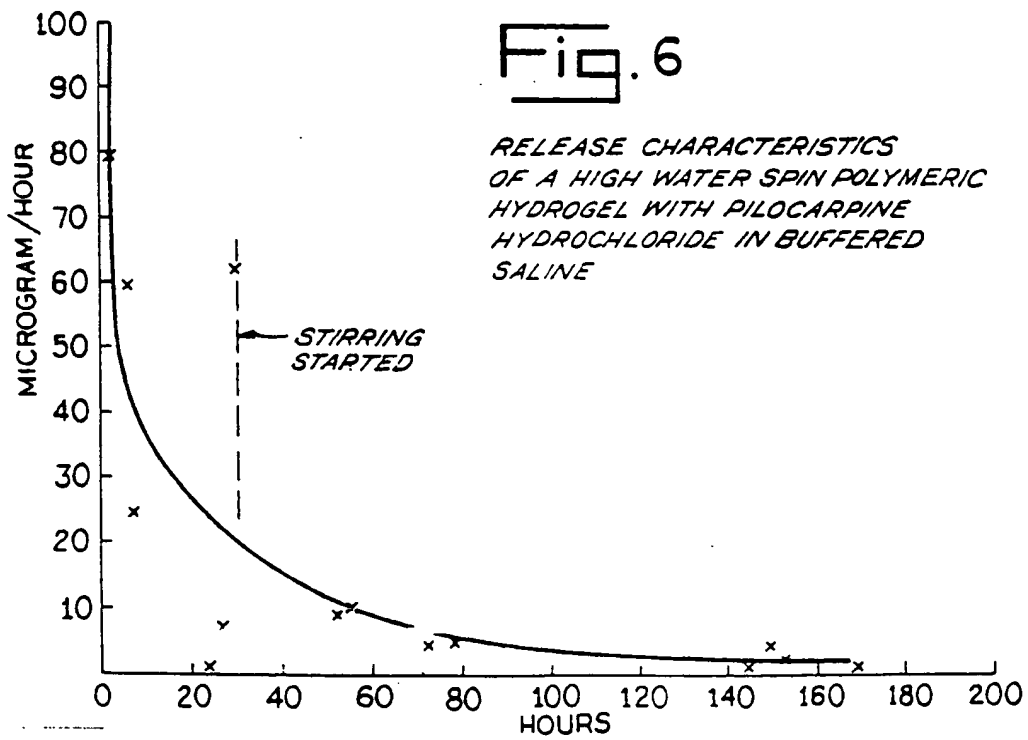
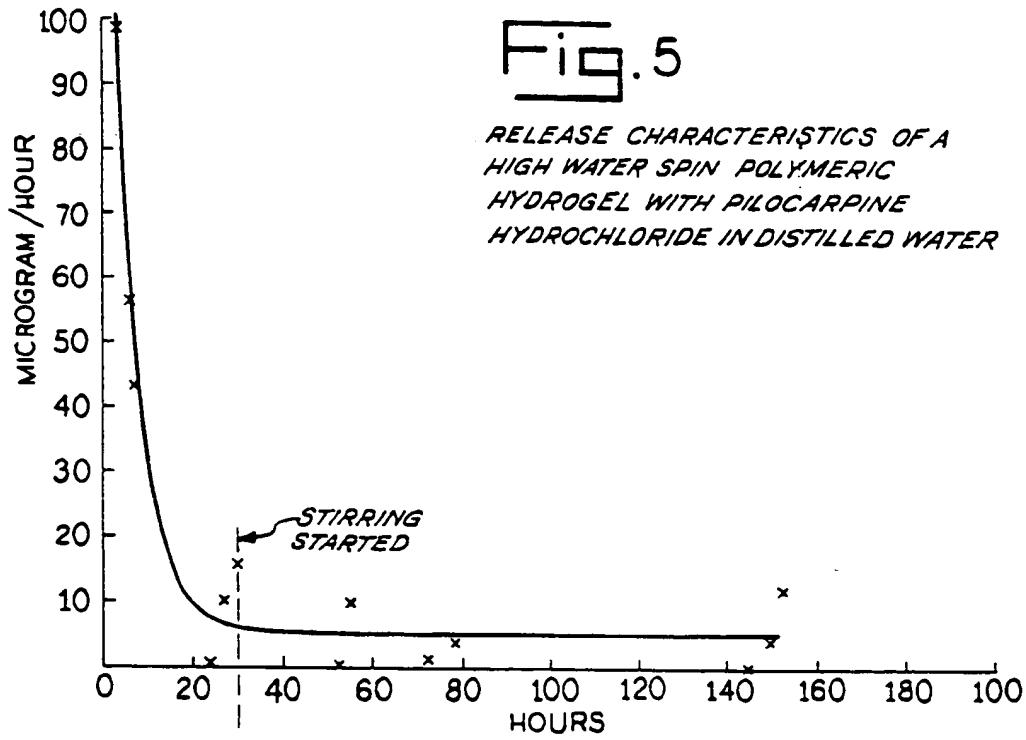
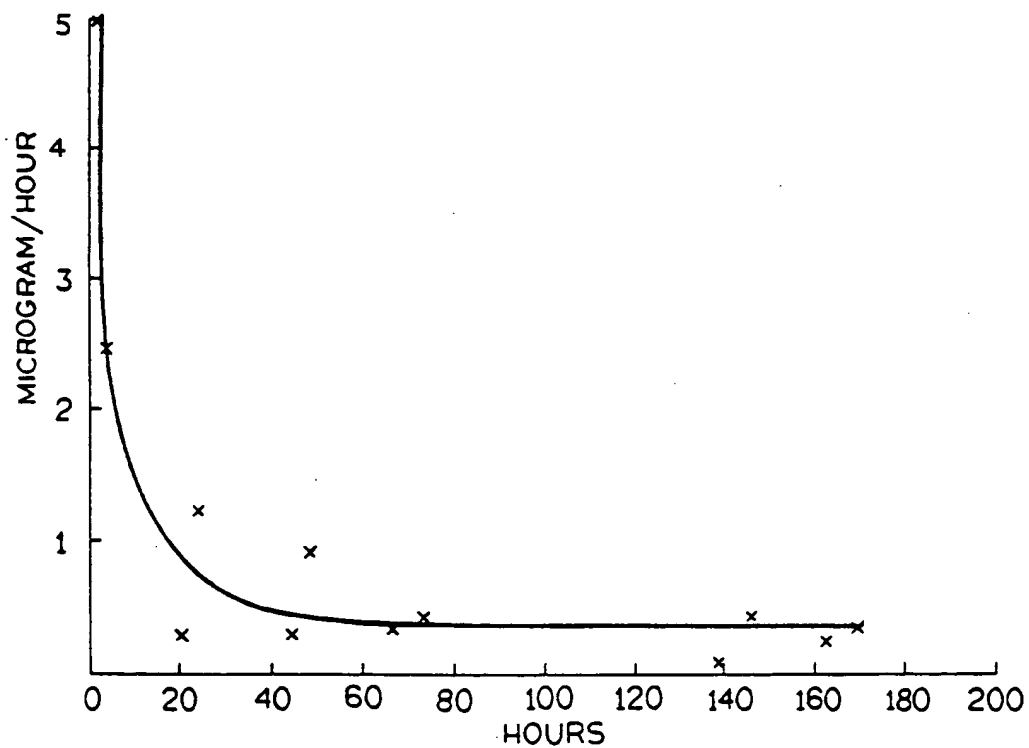
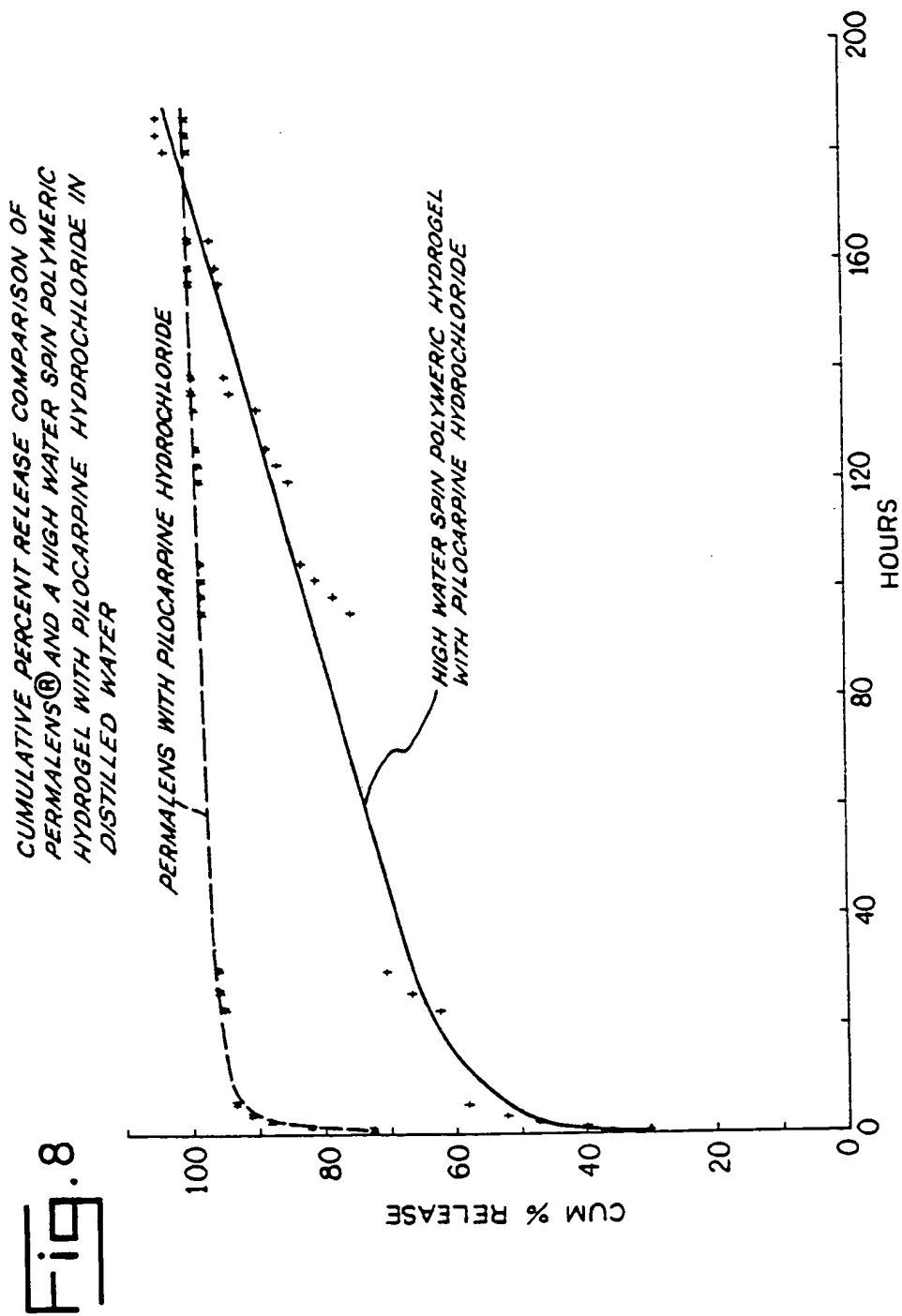


Fig. 7

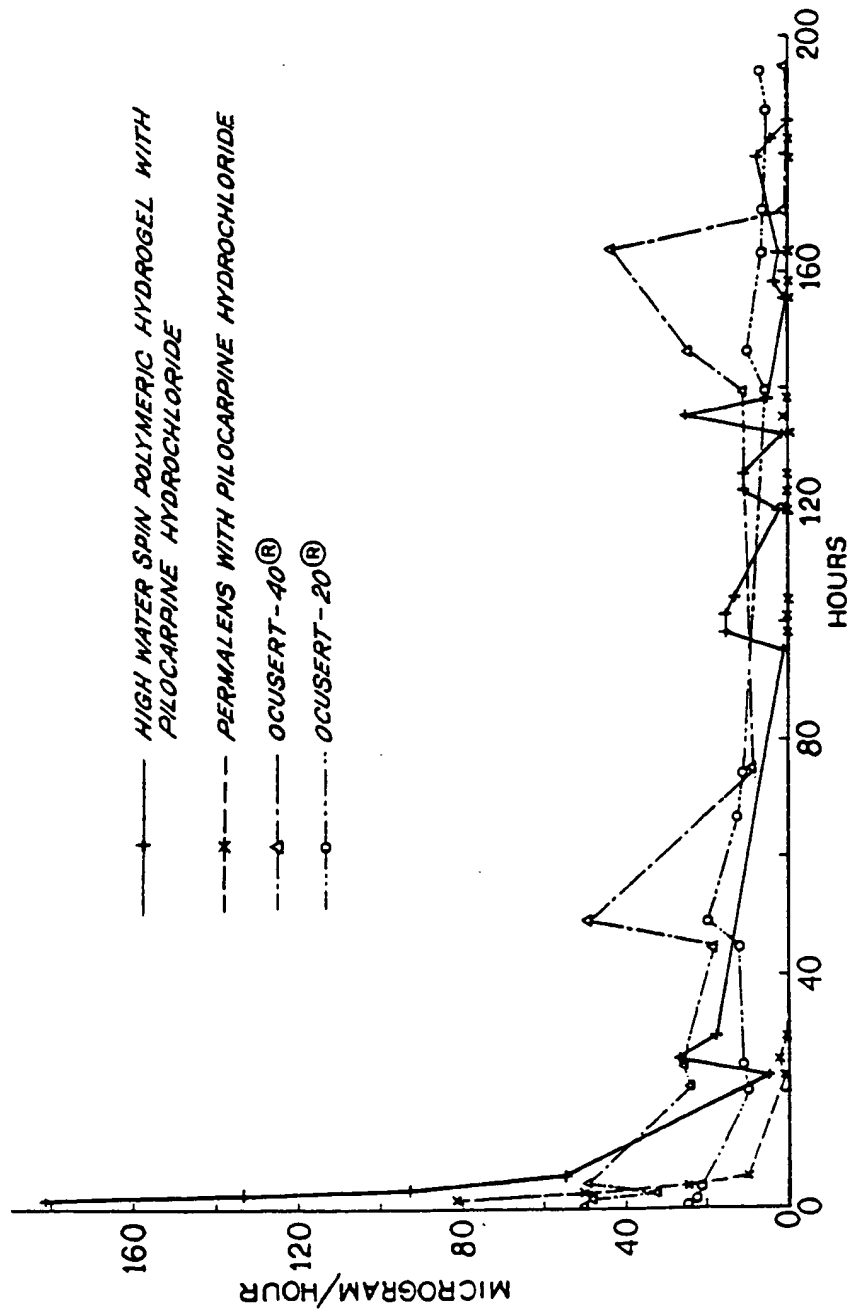
*RELEASE CHARACTERISTICS OF A TRIPLE
SPUN HIGH WATER SPIN POLYMERIC
HYDROGEL COMPRISING POLYMER PLUS
PILOCARPINE HYDROCHLORIDE IN MIDDLE
LAYER IN DISTILLED WATER*





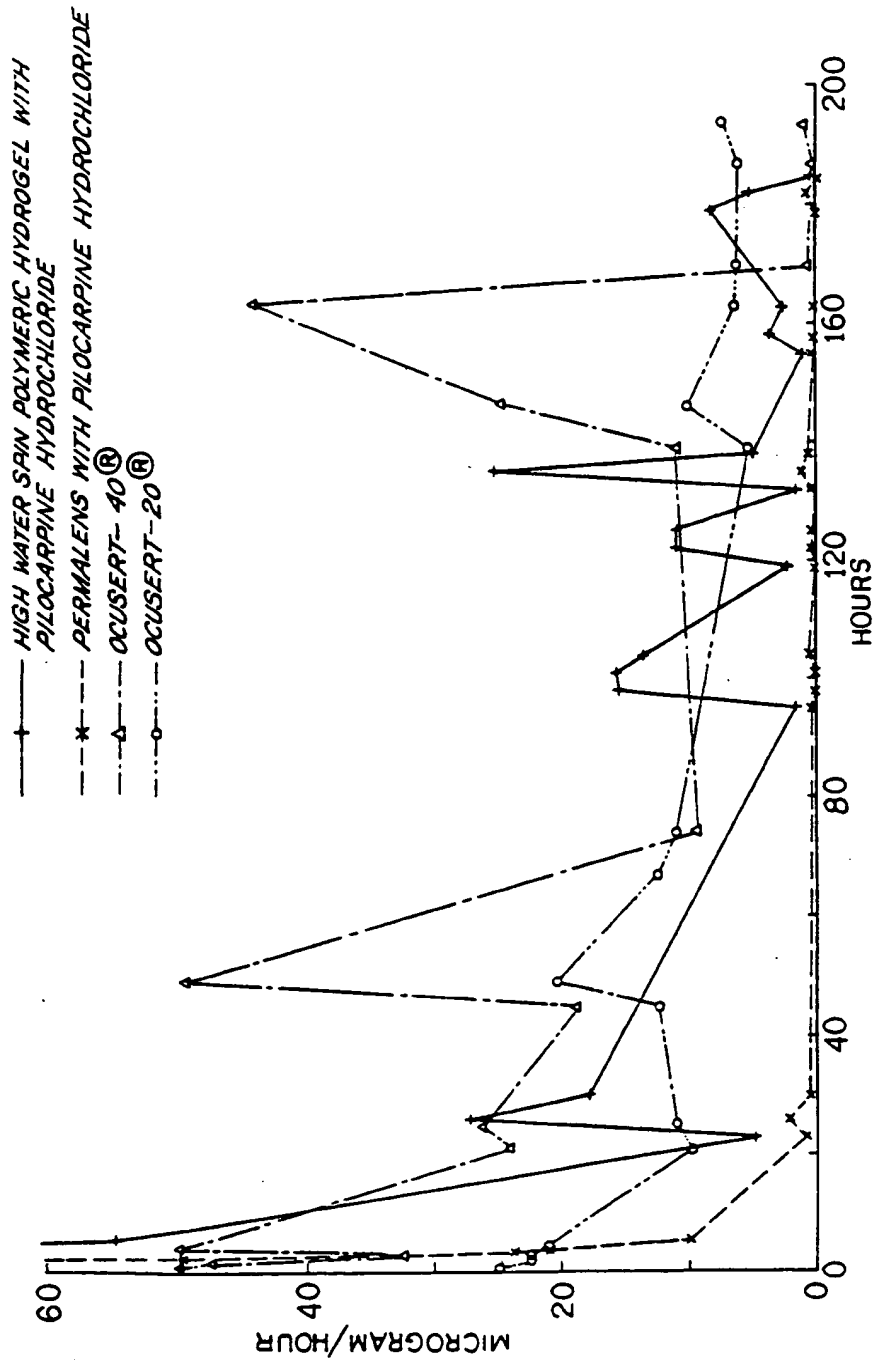
COMPARISON OF THE RELEASE CHARACTERISTICS FOR A HIGH WATER SPIN POLYMERIC HYDROGEL WITH PILOCARPINE HYDROCHLORIDE, PERMALENS[®] WITH PILOCARPINE HYDROCHLORIDE, OCUSERT-20[®] AND OCUSERT-40[®] IN DISTILLED WATER

Fig. 9



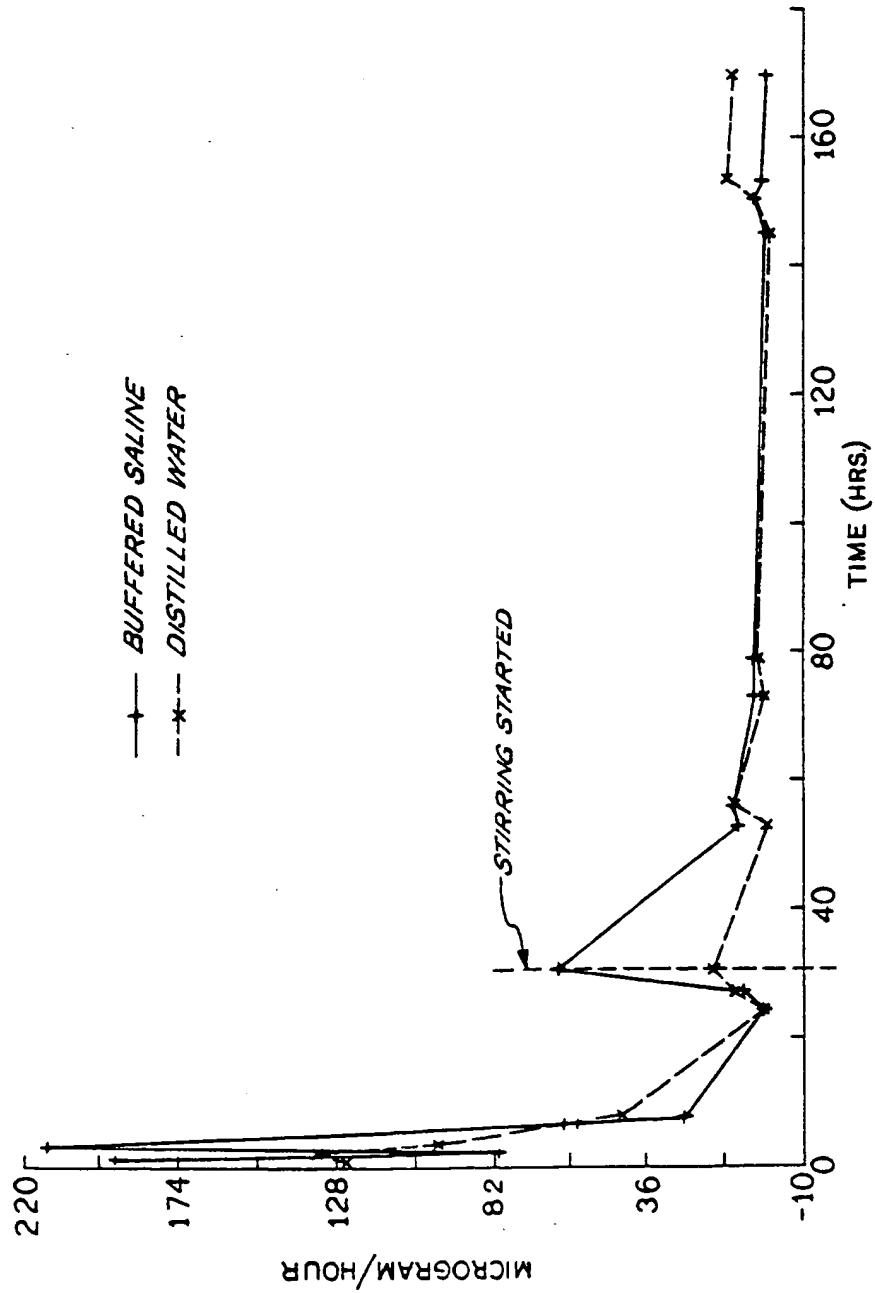
COMPARISON OF THE RELEASE CHARACTERISTICS FOR A HIGH WATER SWIN
POLYMERIC HYDROGEL WITH PILOCARPINE HYDROCHLORIDE, PERMALENS® WITH
PILOCARPINE HYDROCHLORIDE, OCUSERT-20® AND OCUSERT-40® IN DISTILLED
WATER

Fig. 10



RELEASE CHARACTERISTICS FOR A HIGH WATER SWIN POLYMERIC
HYDROGEL WITH PLOCARPINE HYDROCHLORIDE IN DISTILLED WATER
AND BUFFERED SALINE

Fig. 11



RELEASE CHARACTERISTICS FOR A HIGH WATER SPIN POLYMERIC
HYDROGEL WITH PILOCARPINE HYDROCHLORIDE IN DISTILLED WATER
AND BUFFERED SALINE

Fig. 12

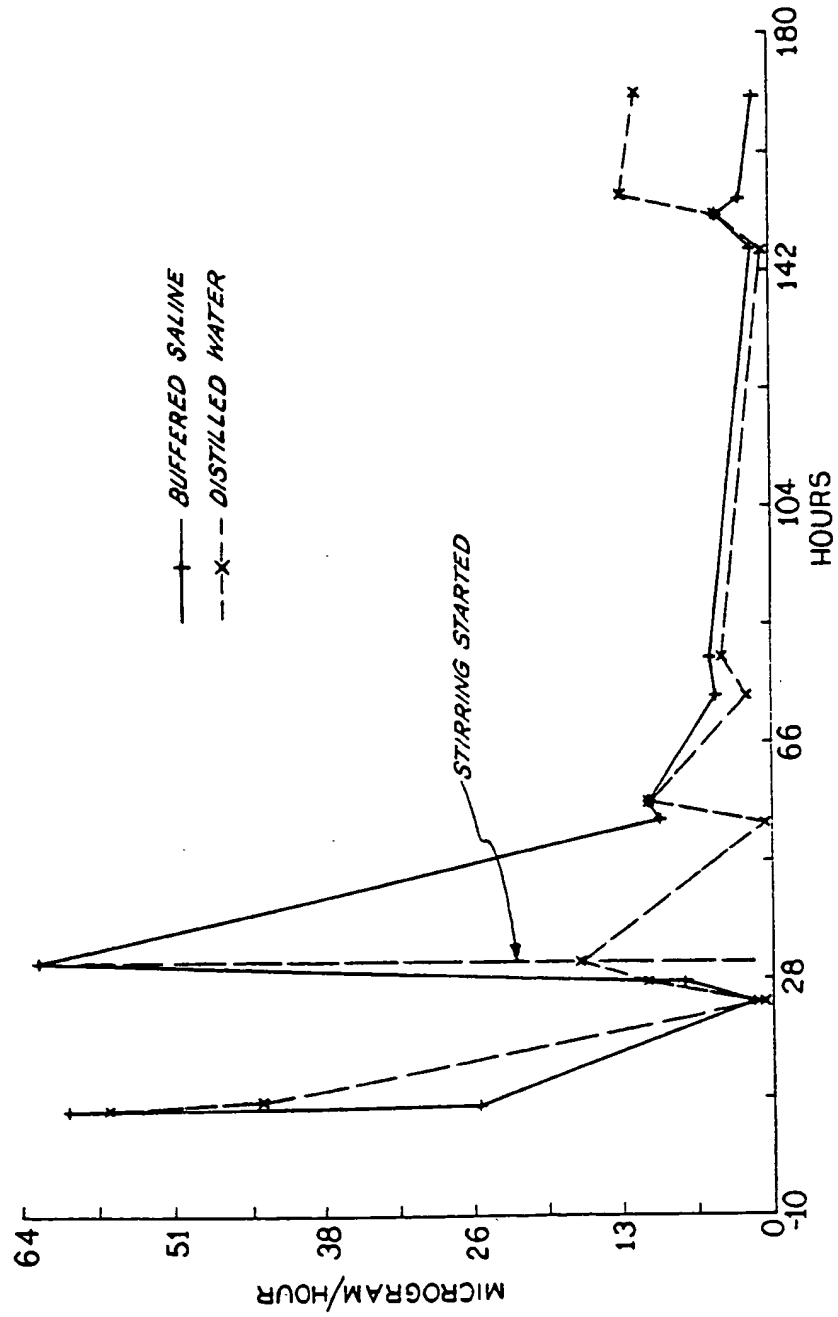
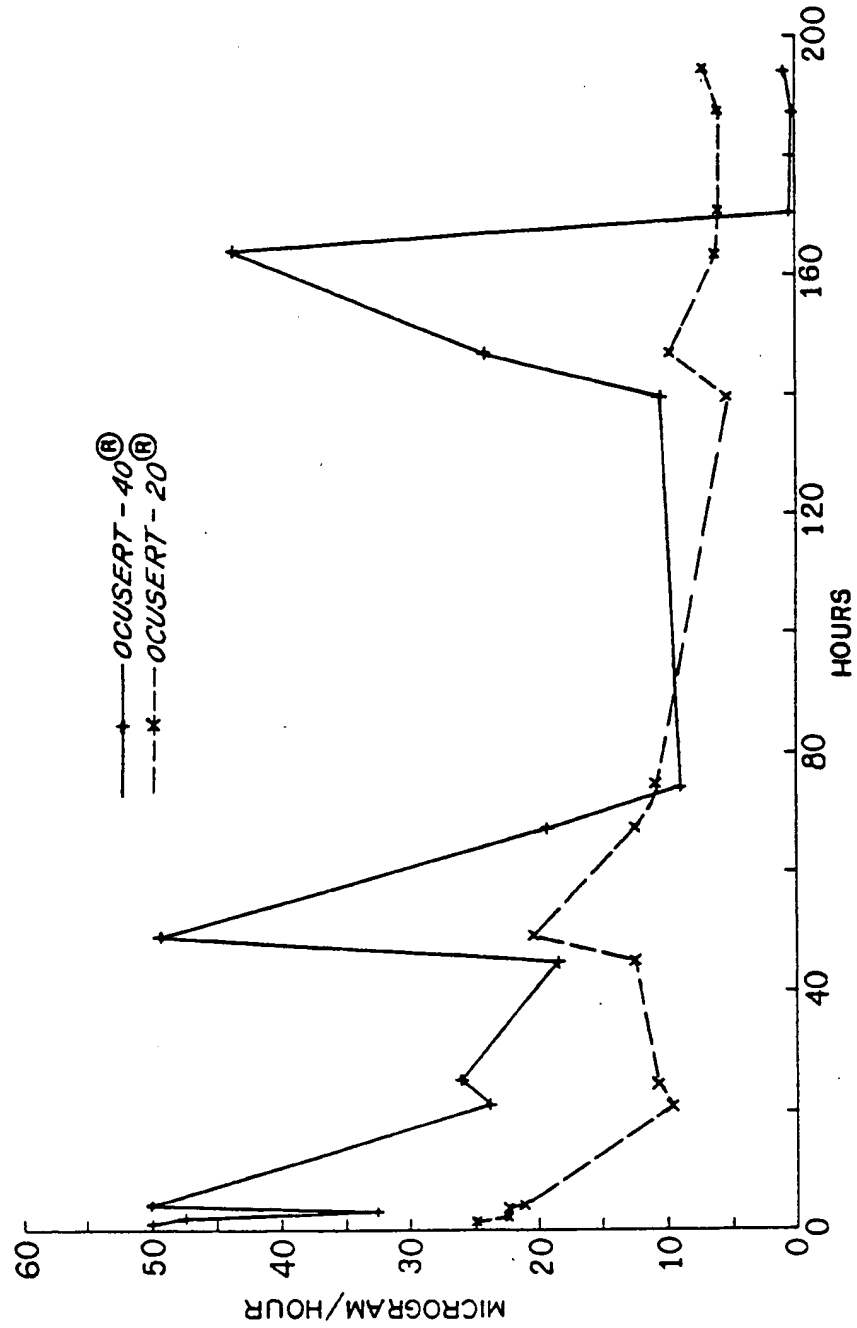


Fig. 13

COMPARISON OF THE RELEASE CHARACTERISTICS FOR
OCUSERT-20® AND OCUSERT-40®



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